eTBLAST

Cancer Res 1991 Dec;51(23 Pt 1);6236-42.

An immunotoxin prepared with blocked ricin: a natural plant toxin adapted for therapeutic use.

J M Lambert
V S Goldmacher

A R Collinson
L M Nadler
W A Blättler

ImmunoGen, Cambridge, Massachusetts 02139.

Ricin, the cytotoxic protein isolated from castor beans, is composed of two subunits, A-chain and B-chain. Ricin intoxicates cells by binding through its B-chain to galactose-terminated oligosaccharides found on the surface of all eukaryotic cells and then transferring its A-chain to the cytosol where it disrupts protein synthesis by inactivating ribosomes. In addition to binding, the B-chain plays an important, but not yet understood, role in the translocation of the A-chain through a cellular membrane to the cytosol. Blocking the two galactose-binding sites of native ricin by chemical modification with affinity ligands created an altered toxin, called blocked ricin, that has at least a 3500-fold lower binding affinity and is more than 1000-fold less cytotoxic than native ricin for Namalwa cells (a Burkitt's lymphoma line) but that has maintained the translocation function of the B-chain and the catalytic activity of the A-chain. Conjugation of blocked ricin to monoclonal antibodies that bind to cell surface antigens creates new cytotoxins that approach the potency of native ricin. These cytotoxins incorporate the three essential functions of natural toxins, i.e., binding to cells, transport through a membrane, and catalytic inactivation of an essential cellular process; but in addition they possess a defined cellular target specificity. Such potent immunotoxins may play an important therapeutic role in cancer treatment. Clinical trials with an anti-CD19-blocked ricin and an anti-CD33-blocked ricin conjugate against B-cell cancers and acute myeloblastic leukemia have begun.

MedlineID: 92034751
PMID: 1718599